

## (*S*)-*o*-*N*-(*N*-Benzylpropyl)aminobenzaldehyde and (*S*)-*o*-*N*-(*N*-Benzylpropyl)aminoacetophenone as Reagents for Asymmetric Synthesis of Threonine

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Chiral aldehydes and ketones, derivatives of proline and piperidine-2-carboxylic acid have been synthesized and their Schiff bases with glycine form copper complexes which were hydroxyethylated with acetaldehyde; decomposition of the complexes obtained gave threonine with an optical purity of up to 97–100% and with threo/allo ratios of up to 19 : 1, and the chiral reagents can be recovered and reused with no loss of optical purity of the threonine.

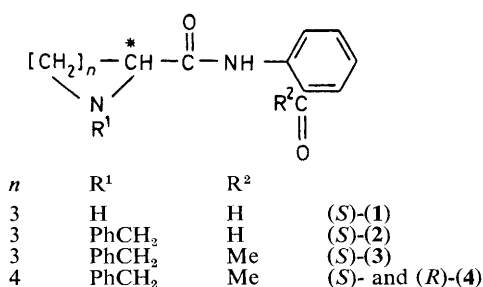
The main disadvantage of chemical methods for the synthesis of (*S*)-amino-acids resides in the necessity to resolve racemic amino-acids and racemise their (*R*)-enantiomers.<sup>1</sup> To eliminate this disadvantage, there has been an intensive search for effective methods for asymmetric synthesis of amino-acids<sup>2</sup> and enantiomeric enrichment of racemic  $\alpha$ -amino-acids, obviating the resolution stage.<sup>3–5</sup> Earlier we reported on the use of a chiral aldehyde [enantiomers of 1-(*N,N*-dimethylaminomethyl)-2-formylcymanthrene] for asymmetric synthesis of ThrGly from GlyGly with an optical purity of 98%.<sup>5</sup> However, this cymanthrene derivative carries out asymmetric transformations only with dipeptides and cannot be used for direct asymmetric synthesis of amino-acids.

We report here the synthesis of the chiral reagents (1)–(4), which are derivatives of (*S*)-proline and (*S*)- or (*R*)-piperidine-2-carboxylic acid, and on their use for the asymmetric synthesis of threonine from glycine and acetaldehyde.

Compounds (2)–(4) were obtained in 30–50% yields by condensation of the hydrochlorides of *N*-benzylpropyl chloride or *N*-benzylpiperidine-2-carbonyl chloride with *o*-aminobenzaldehyde or *o*-aminoacetophenone in the two-phase system CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O at 25 °C, with the water layer at pH 8. Compound (1) was obtained by condensation of *N*-formylproline with *o*-aminobenzaldehyde, the *N*-formyl group being removed in the subsequent formation of the copper complex of the Schiff base with the amino-acid.

The Schiff bases of compounds (1)–(4) with amino-acids in MeOH give the complexes with copper(II) in Scheme 1. The structures were assigned by physical and chemical methods. The copper complexes of the Schiff bases of reagents (1)–(4) with Gly in methanolic sodium methoxide react with acetaldehyde, giving a mixture of intermediate threonine complexes, from which threonine can be isolated with chemical yields of 80–100% and the initial reagents (1)–(4) with recoveries of 70–90% (Scheme 1). The asymmetric yield of threonine and the threo/allo ratio are presented in Table 1.

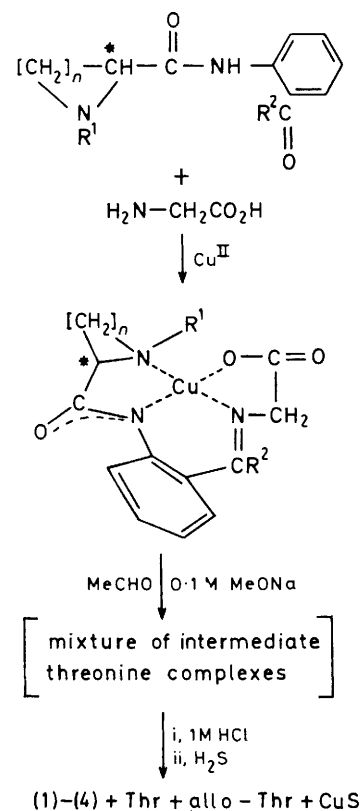
In a typical experiment, to a stirred solution of (*S*)-(3) (1 mmol) in methanolic NaOMe (0.14 M; 10 ml) at room temperature was added a solution of CuSO<sub>4</sub>·5H<sub>2</sub>O (1.1 mmol) in water (3 ml), followed by a solution of Gly (1.1 mmol) in methanolic NaOMe (1 M; 1.1 ml), and the solution was then stirred for a further 15 min. The solution was diluted with



**Table 1.** Enantiomeric composition of threonine obtained in the hydroxyethylation of the copper(II) complexes of (1)–(4) and Gly.

Reagent	Reaction <sup>a</sup> time/h	Thr/ allo-Thr	Enantiomeric purity, % <sup>b</sup>	
			Threonine	Allothreonine
( <i>S</i> )-(1)	1	2.8	4 ( <i>R</i> )	6 ( <i>S</i> )
( <i>S</i> )-(1)	4	2.5	3 ( <i>R</i> )	Racemate
( <i>S</i> )-(2)	0.5	4.9	58 ( <i>R</i> )	12 ( <i>S</i> )
( <i>S</i> )-(2)	1	5.6	56–60 ( <i>R</i> ) <sup>c</sup>	Racemate
( <i>S</i> )-(2)	4	5.8	61 ( <i>R</i> )	16 ( <i>R</i> )
( <i>S</i> )-(2)	19 <sup>d</sup>	9.7	65 ( <i>R</i> )	30 ( <i>R</i> )
( <i>S</i> )-(3)	1	3.8	92 ( <i>R</i> )	100 ( <i>R</i> )
( <i>S</i> )-(3)	4	19	97–100 ( <i>R</i> )	100 ( <i>R</i> )
( <i>R</i> )-(4)	1	10	89 ( <i>S</i> )	90 ( <i>S</i> )
( <i>R</i> )-(4)	3	12	92 ( <i>S</i> )	100 ( <i>S</i> )
( <i>S</i> )-(4)	3	11	92 ( <i>R</i> )	100 ( <i>R</i> )

<sup>a</sup> Complex concentration = 0.1 M, MeCHO/complex = 50; in 0.2 M MeONa at 25 °C under Ar. <sup>b</sup> According to g.l.c.<sup>6</sup> <sup>c</sup> The results of four experiments are within this range. <sup>d</sup> Reaction at –5 °C.



**Scheme 1**

H<sub>2</sub>O and extracted with CHCl<sub>3</sub>. Upon evaporation, (*S*)-(3)-Gly-Cu<sup>II</sup> was obtained in quantitative yield (0.44 g). To a solution of this complex and MeCHO (50 mmol) in anhydrous MeOH (5.2 ml), methanolic NaOMe (1 M; 2 ml) was added under argon, and the mixture was kept at 25 °C for 1 h. HCl (1 M) was then added, and the resulting solution was diluted with H<sub>2</sub>O and treated with H<sub>2</sub>S. CuS was filtered off, and washed with H<sub>2</sub>O and CHCl<sub>3</sub>. The combined water layers were neutralized and extracted with CHCl<sub>3</sub>. The combined organic layers were evaporated giving 0.28 g (85% recovery) of (*S*)-(3). The amino-acids were isolated from the water solution on a 'Dowex-50' resin in 80–100% yield (g.l.c.).

The retrieved (*S*)-(3) can be repeatedly used for the asymmetric synthesis of Thr with no loss of optical purity of the latter.

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